



Letter

Recurrent angioedema after naproxen use in a patient stabilized with losartan

Allergic reactions that result from concomitant drug use are understood yet potentially overlooked risk factors for angioedema. Nonsteroidal anti-inflammatory drugs (NSAIDs) in particular have been noted to trigger angioedema in patients with associated risk who are stabilized with other agents.^{1,2} Previous reports have described cases of angioedema after NSAID administration in patients stabilized on angiotensin-converting enzyme (ACE) inhibitors; however, detailed reports in patients receiving angiotensin receptor blockers (ARBs) are lacking.^{1–4} We present a case of recurrent angioedema following naproxen use in a patient stabilized on losartan.

A 74-year-old white male stabilized on losartan, 50 mg reported developing lip swelling on 2 occasions following naproxen use. On both occasions, symptoms developed shortly after naproxen administration, persisted for several hours, and resolved without sequelae. Urticaria was not present. Before initiating losartan, the patient had tolerated concomitant use of naproxen and lisinopril without incident. Three months earlier losartan was initiated when the patient developed an ACE inhibitor cough after several years on lisinopril. Medical history included hypertension, hyperlipidemia, chronic renal insufficiency, benign prostatic hyperplasia, esophageal reflux, allergic rhinitis, and chronic knee pain, as well as cutaneous allergic reactions to penicillin (rash) and sulfa drugs (hives). Other medications included felodipine extended release, hydrochlorothiazide, simvastatin, omeprazole, cetirizine, and daily aspirin (81 mg). Physical examination findings were unremarkable at the time of presentation. Relevant laboratory findings were as follows: estimated glomerular filtration rate, 45 mL/min per 1.73 m²; serum creatinine, 1.49 mmol/L; and blood urea nitrogen, 27 mg/dL. Because of concerns of angioedema, losartan was discontinued, and the patient has since continued to use naproxen episodically without incident.

Historically, ARB-induced angioedema was not believed to be bradykinin mediated because these agents primarily inhibit angiotensin II binding at angiotensin type 1 receptors. However, ARBs have been found to increase angiotensin II, which may raise activity at angiotensin type 2 receptors and bradykinin levels. Specifically, losartan, 50 mg, has been found to increase bradykinin levels in hypertensive patients.⁵

To our knowledge, this is the first detailed report of angioedema following NSAID use in a patient stabilized on an ARB. In a cohort of 64 patients with medication-related angioedema, Banerji et al³ reported a single case in a patient receiving aspirin and an ARB. Similarly, Malde et al⁴ noted that 38% of patients with medication-related angioedema were receiving concomitant therapy with an NSAID and an ACE or ARB. As with our patient, 22% had allergies to other medications, including penicillin (14%) and sulfonamides (3%). Advanced age, ACE inhibitor cough, and environmental allergies are also considered risk factors for angioedema.

We believe the recurrent angioedema reported by our patient is most likely ARB related. NSAID-induced angioedema is often accompanied by urticaria, and our patient tolerated both naproxen and low-dose aspirin while receiving lisinopril and upon discontinuation of losartan. In addition, the duration of reported symptoms is consistent with the relatively short half-lives of losartan and its active metabolite 5-carboxylic acid.

Why angioedema did not occur on coadministration with naproxen and lisinopril is unclear but may suggest a dose-related phenomenon. Although the risk of ACE inhibitor angioedema is generally believed to be independent of dose, Iron et al⁶ hypothesized a potential dose relationship with valsartan. The authors describe a patient stabilized on valsartan 160 mg/d, who developed angioedema shortly after the dose was increased to 360 mg/d which resolved upon dose reduction. Plasma concentrations of losartan and 5-carboxylic acid are increased by 50% to 90% in patients with mild-to-moderate renal dysfunction.⁷ Likewise, previous reports have discussed episodes of losartan-induced angioedema in patients with renal insufficiency.⁸ It is possible that naproxen administration impaired renal function, prompting a dose-dependent reaction in our patient who had multiple existing risk factors for angioedema. Despite the presence of chronic renal insufficiency, renal function remained stable when the patient was transitioned from lisinopril to losartan. This coupled with the fact that he had previously tolerated concurrent use of naproxen, aspirin, and lisinopril further supports the hypothesis that these reactions were primarily an effect of concomitant losartan and naproxen use and not reflective of his underlying chronic kidney disease. The Naranjo adverse drug reaction scale⁹ indicates that coadministration of naproxen and losartan was a probable cause of angioedema in our patient (score 5). Previous publications have highlighted the importance of concomitant drug use and risk of angioedema.^{1–4} Given the relatively new availability of generic ARBs and widespread use of over-the-counter and prescription NSAIDs, awareness of this potential adverse event is critical.

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